Editorial

The eligibility of primary tumor resection for *de novo* stage IV breast cancer patients

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There are many retrospective reports to indicate the survival benefit of primary tumor resection for *de novo* stage IV breast cancer. Moreover, several comprehensive reviews have described significant differences in survival time (hazard ratio of ~0.6) (1,2). However, retrospective reports include numerous biases. Patients undergoing surgery might be in good condition for surgery, while those not receiving surgical treatment might have poor overall condition. In addition, details regarding the efficacy and the disease control rate for systemic therapy are lacking. Currently, we don't know the most appropriate timing for surgery or patients' status. One of the most important questions is whether the best timing for primary tumor resection is before or after primary systemic therapy. We can determine the indications of surgery according to the efficacy of systemic therapy. Moreover, we can completely remove the locally advanced primary tumor with muscle and/or skin invasion after tumor volume reduction by systemic therapy. Lane *et al.* reported the results of patterns of surgical care and their association with overall survival among a contemporary cohort of women with stage IV breast cancer (3). They reported that surgical resection of the primary tumor occurs in almost half of women with stage IV breast cancer alive 1 year after diagnosis. Primary tumor resection for *de novo* stage IV breast cancer patients, especially after systemic therapy (before systemic therapy: hazard ratio, 0.62–0.73; after systemic therapy: hazard ratio, 0.56; P<0.001), was independently associated with improved adjusted overall survival when compared to systemic therapy alone. However, there were no details about the response to primary systemic therapy. The Translational Breast Cancer Research Consortium (TBCRC) reported results of a prospective cohort study of stage IV breast cancer patients (4). There was no significant prognostic effect of primary tumor resection for responders to primary systemic therapy. We need to confirm the indications and timing of surgery by prospective randomized trials.

Five prospective randomized trials have analyzed the efficacy of primary tumor resection for stage IV breast cancer (*Table 1*) (5). Three have reported final results, and the others are still currently enrolling patients or following up. The first results were from the Indian trial (6). The efficacy of primary tumor resection for Stage IV breast cancer patients with sensitivity to primary systemic therapy was evaluated, and they could not indicate the prognostic efficacy of surgery. A Turkish trial (MF07-01) (7) and the ABCSG-28 (POSYTIVE trial) (8) evaluated prognostic effects of surgery as the primary treatment before systemic therapy. The Turkish trial suggested a positive effect of primary surgery; however, the POSYTIVE trial could not demonstrate an OS benefit. We cannot get the best evidence from the prospective studies so far because these trials have had limitations in the evaluations; In the Indian trial, systemic therapies were not selected according to breast cancer subtypes. Anti-HER2 molecular targeted therapies were not used for patients with HER2-positive tumors, and very few patients with ER-positive tumors received hormone administration as primary

Table 1 Randomized clinical trials

Country (trial group)	Trial number	Accrual period (situation)	N	Initial therapy	Primary endpoint
India	NTC00193778	2005–2012 (completed)	350	Systemic therapy	Overall survival
Japan (JCOG)	UMIN000005586 (JCOG1017)	2011–May 2018 (completed)	500/410→600/410	Systemic therapy	Overall survival
USA and Canada (ECOG)	NCT01242800 (ECOG2108)	2011–2015 (completed)	880/660→368/258	Systemic therapy	Overall survival
Turkey	NCT00557986 (MF07-01)	2008–2012 (completed)	281	Surgery	Overall survival
Austria (ABCSG)	NCT01015625 (ABCSG 28)	2010–2015 (early stopped)	256→90	Surgery	Overall survival

systemic therapy. The Regatta trial for stage IV gastric cancer reported similar results. Gastrectomy followed by chemotherapy yielded no survival benefit compared with chemotherapy alone (9). The authors suggested one of the reasons was reduced compliance with chemotherapy after surgery due to adverse events like weight loss. We think the most important treatment of metastatic cancer is effective drug from these trials' results.

Moreover, discontinuation of effective systemic chemotherapy after randomization might result in a poorer outcome in distant progression-free survival in the patients with surgery group. This result follows the pattern of previous reports. Folkman demonstrated that the primary tumor actively secretes angiostatin, which suppresses the angiogenic activity of metastatic cancer, and that resection of the primary tumor removes that suppression, and thus increases angiogenesis and growth of metastatic lesions (10). Fisher demonstrated that animals with metastatic disease were immunologically compromised, and that surgical stress releases growth factors, which in turn stimulate proliferation of metastasized cancer cells (11). The POSYTIVE trial reported similar results; however, there were no details about systemic therapy after randomization. More data on systemic treatment are needed to evaluate this clinical question. Given the POSYTIVE trial lacking the statistical power, and the Turkish trial has not published some details, a discussion about the discordance of results between these trials is warranted.

The most important treatment for stage IV breast cancer patients is systemic therapy. The improvement of systemic drugs prolongs survival absolutely. Local therapy, including surgery, is one of the choices for metastatic breast cancer treatment. Currently, there are no definitive results to evaluate the prognostic effect of surgery. The Turkish trial indicated a positive effect, but the Indian trial reported a worse effect of surgery for these patients. From the results of these prospective studies, primary tumor resection for *de novo* stage IV breast cancer cannot be recommended to all patients routinely. The impact of surgery on survival is not so large for *de novo* stage IV breast cancer. We need to consider eligibility for surgery and planning integrated treatment strategies, including local therapy, according to breast cancer subtype, metastases and the patient's condition. Our aim should be to devise the most effective treatment strategies for individual cancer patients, employing drugs, surgery and radiation, alone or in combination. The treatment goals for stage IV breast cancer are to prolong the patient's survival time and to control symptoms.

The Japan Clinical Oncology Group (JCOG 1017) and Eastern Clinical Oncology Group (ECOG 2108) are enrolling and following patients for a phase 3 trial (*Figure 1*). In these trials, patients received the most up-to-date standard systemic therapy available before and after randomization, and also the most advanced form of imaging examination available before treatment. It is anticipated that the aforementioned trials will resolve current controversies and provide many eagerly awaited answers.

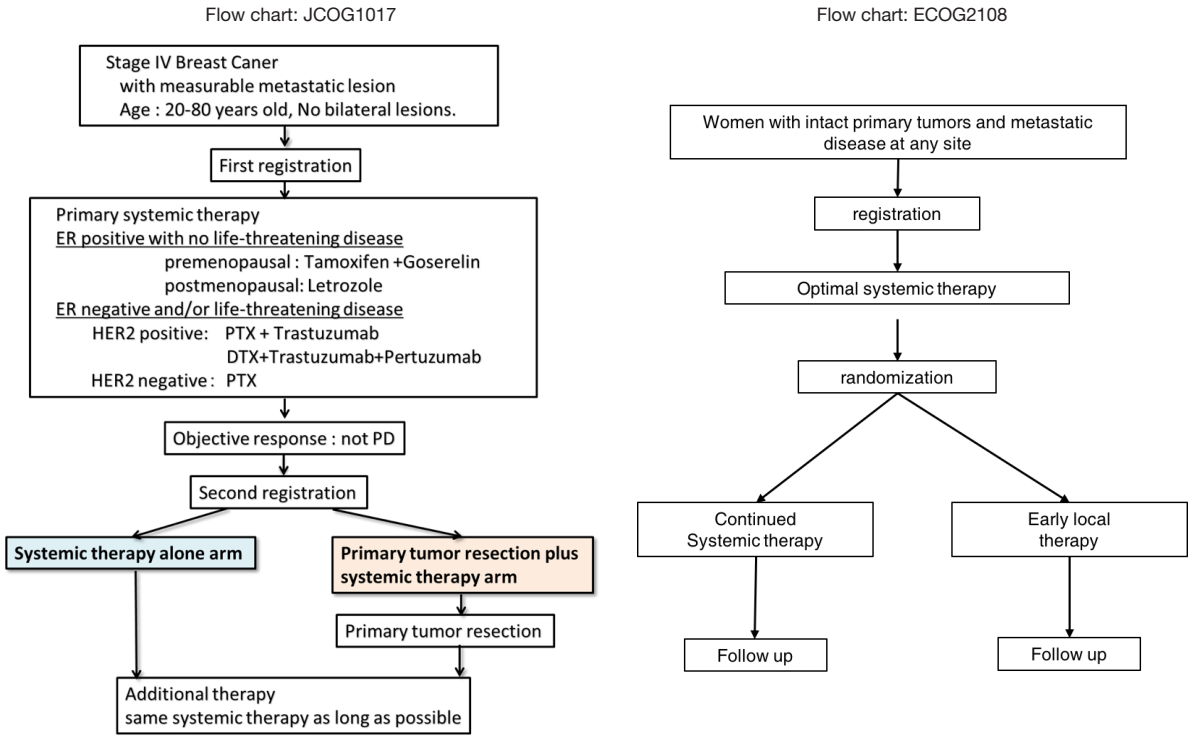

Figure 1 Flow charts of JCOG1017 (UMIN00005586) (5) and ECOG2108 (NCT01242800) (ClinicalTrials.gov).

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Footnote

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